Absence of Intersystem Crossing in 1,4-Didehydrobenzene

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The rate of singlet-to-triplet intersystem crossing in 1,4-didehydrobenzene (the biradical produced as a reactive intermediate in the thermal cycloaromatization of enediynes), cannot be increased by the application of an external magnetic field. The rate of product formation and the distribution of stable products of 2,3-di-*n*-propyl-1,4-didehydrobenzene thermolysis is unchanged at magnetic flux densities in the range 0–2000 G and at 66 000 G. Similarly, the rate of thermolysis of an unsymmetrical enediyne is insensitive to magnetic field flux in the same range. This finding precludes the modulation of enediyne reaction rates in pharmaceutical and synthetic pursuits.

The discovery and characterization of the naturally occurring enediyne antitumour antibiotics neocarzinostatin, esperamicin, calicheamicin, dynemicin and kedarcidin have sparked a renewed interest in the Bergman cycloaromatization reaction.[1–5] These antitumour antibiotics have served as models for synthetic DNA cleaving agents[6] based upon the reactive 1,4-didehydrobenzene (benzene-1,4-diyl) intermediate. Similarly, the synthetic utility of the enediyne cycloaromatization reaction for constructing multiple ring systems has drawn much attention as well.[7] Our interest in this class of compounds stems from questions about the electron spin multiplicity and bonding in the 1,4-didehydrobenzene intermediate, and the possibility of manipulating biradical reaction rates and product distributions by changing the electron spin multiplicity.

Bergman first demonstrated the thermal ring closure of an enediyne to yield the 1,4-didehydroaromatic biradical intermediate and showed that it is a reversible process in reactions that are not highly exergonic.[8] The ring may open in two ways: to reform the starting enediyne or to form a rearranged enediyne. Conservation of electron spin requires that this ring opening proceed from the singlet electron spin state of the 1,4-biradical. If the triplet manifold of the biradical intermediate were significantly populated, the ring opening process would be inhibited and the lifetime of the biradical would be extended. A competing intermolecular trapping process (H atom abstraction from solvent or similar) would then be favoured over ring opening.

Investigations of the reactive spin state of 1,4-didehydrobenzene strongly suggest that thermolysis of diethynylalkenes produces exclusively the singlet biradical and that intersystem crossing (ISC) from the singlet (S) to the triplet (T) reaction surface does not occur at a rate comparable to intermolecular H-atom abstraction.[9] The cage to escape (C:E) ratio of the 2,3-di-*n*-propyl-1,4-didehydrobenzene biradical reacting with cyclohexa-1,4-diene (as intermolecular H-atom donor) does not vary as the concentration of intermolecular trap is changed over a 100-fold range.[9b] The invariance of C:E with respect to the concentration of intermolecular trap suggests ISC is either much faster than opening of the 1,4-didehydrobenzene ring (*ca.* 10^9 s^{-1}) or the more likely case that ISC is much slower than 10^9 s^{-1}.[9b] The C:E ratio was also unchanged in a heavy-atom solvent, thus providing a further indication that ISC from the S to the T reaction surface is unimportant on the timescale of the reaction.[10] Direct observation of an EPR signal for 1,4-didehydroanthracene at 8 K was also unsuccessful.[11]

In order for ISC to occur in systems of relatively low energy (*i.e.*, thermolysis biradicals with singlet ground states), the S–T energy gap, ΔE_{ST}, must be small. Diverse computational studies have estimated ΔE_{ST} to be 0.5–2.0 kcal mol^{-1} in 1,4-didehydrobenzene.[12a–e] Clearly, the S and T spin states are energetically accessible *if a mechanism exists to mix the S and T reaction surfaces.*

Hyperfine Coupling (HFC) Induced ISC.—The rate of ISC (k_{isc}) in reactions with spin-correlated biradicals can be altered by external magnetic fields (laboratory electromagnets) and endogenous magnetic fields (arising from HFC to a non-zero nuclear spin).[13] At the geomagnetic field of 0.5 G, HFC between the unpaired electron and a nucleus with non-zero magnetic moment provides a non-adiabatic pathway to mix the singlet and triplet reaction surfaces. When a magnetic field comparable to the hyperfine coupling constant (typically 10–30 G for organic radicals) is applied, HFC is decreased and mixing between the S and T spin states is decreased. In a biradical produced in the S state, HFC would lead to population of the triplet surface and a net decrease in the return to starting material (analogous to cage recombination).

Level-crossing Induced ISC.—In biradicals with a fixed separation between the centres of unpaired electron density, a specific crossing of the S and T_{-1} surfaces can occur as the three triplet spin states, T_0, T_{+1} and T_{-1}, are split by the Zeeman interaction energy. This increase in S–T mixing decreases at higher magnetic field. In a biradical produced in the S state, this increase in ISC would decrease the formation of recombination products by populating the triplet reaction manifold.

Δg *Induced ISC.*—In biradicals with unequal Lande *g*-values for the unpaired electron spins, the difference in precession rates in the magnetic field differs by Δg. The rate k_{isc} is given by $\Delta g \beta \boldsymbol{B}$, where β is the Bohr magneton and $\boldsymbol{B}$ is the applied magnetic flux density. For a biradical produced in the S state, the 'Δg' mechanism will populate the T state at $\boldsymbol{B} > 0$ and result in a net decrease in recombination products. The reader will note that the net result of the HFC and Δg processes are opposite (*i.e.*, when starting from the singlet biradical, one process increases recombination, while the other process decreases recombination to starting material).

Although Lockhart and Bergman have shown that the C:E ratio for reaction of the singlet 1,4-didehydrobenzene biradical is unchanged by heavy-atom solvents (indicating ISC does not compete with biradical trapping), we were intrigued by the possibility of controlling the reactivity of the 1,4-didehydrobenzene biradical by populating the T state through magnetic field induced ISC. To test this possibility, we have investigated the C:E ratios and absolute reaction rates of symmetric and asymmetric enediynes as a function of magnetic field. For symmetric enediynes, $\Delta g = 0$ in the corresponding biradical, whereas $\Delta g \neq 0$ in asymmetric enediynes.

Experimental

Materials.—All compounds were reagent grade or better and were used without further purification unless specified other-

wise in the published synthetic procedure. All solvents were purified prior to use by standard methods.[14] Compound **1** was synthesized according to the procedure of Bergman,[9a,b] compound **6** was synthesized by the method of Semmelhack,[15] and compound **8** was a gift from Professor Janet W. Grissom.[7c] Known compounds were identified by a comparison of their NMR spectra with published data.

Physical Measurements and Data Analysis.—Thermolysis products were analysed by GLC on a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector, a Shimadzu CR501 Chromatopac integrator, and a DB-1 megabore capillary column (0.53 mm × 30 m). Kinetic isotherms were fitted to the integrated first-order rate equation by nonlinear methods.

Thermolysis Apparatus and Procedure.—Details of the product analysis of the thermolysis of **1** and **8** are fully described elsewhere.[9a,b,7c] Naphthalene was identified as the product of thermolysis of **6** by comparison with an authentic sample. A sample for each time point was prepared by flame-sealing a 10 μl aliquot of the indicated solution in a Pyrex capillary (1.5 × 30 mm) under vacuum at −196 °C. Samples were thermolysed sequentially for times varying from 1 min to 180 min such that the longest time point exceeded $3\tau_{1/2}$. Each sample represented one time point in the kinetic determination. Immediately upon removal from the heating apparatus, the ampoules were cooled to −78 °C to halt the reaction. The disappearance of starting material was monitored as a function of time by GLC analysis of the contents of each ampoule. The heating apparatus consisted of a Lauda NBS-D8 circulating heating bath filled with 18 dm^3 of dibutyl phthalate as the heating fluid. Temperature control to ±0.1 °C was accomplished by a proportioning digital temperature controller. The heating fluid was circulated through a silvered Pyrex vacuum-jacketed Dewar placed in the air gap of a laboratory electromagnet with 12.5 cm diameter cylindrical poles. The magnetic flux density in the volume occupied by the sample was homogeneous to better than 1% and the long-term stability of the applied field exceeded 0.1%. The alternating magnetic field component caused by unfiltered AC ripple was less than 1 ppm RMS. The magnetic flux density was monitored with an F. W. Bell (model 4048) digital teslameter.

Results

Compounds **1**, **6** and **8** were thermolysed at the indicated temperature and magnetic flux density. Cyclohexa-1,4-diene (CHD) was present in excess to serve as a hydrogen atom donor. In the absence of hydrogen atom source, a heterogeneous product distribution was observed including a considerable amount of darkly coloured polymer. The kinetic results obtained by following the disappearance of starting material are summarized in Fig. 1. The first-order rate constants for disappearance of starting material were found not to vary with the magnetic flux density over the range of this study. The product distribution in the thermolysis of **1** was also invariant with magnetic flux density (Fig. 2).

Enediyne **1** thermolyses cleanly and exhibits first-order kinetics at 156 °C. The reaction mechanism elucidated by Bergman and co-workers is shown in Scheme 1.[9] In the rate-determining step, spin conservation requires that **1** cyclize to the S state of the 1,4-didehydrobenzene biradical intermediate **2**. Ring opening from singlet **2** yields the starting enediyne **1**, or the rearranged enediyne **3**. Acyclic enediynes substituted at both alkyne functionalities are reluctant to cyclize, thereby making the ring opening of **2** to **3** an irreversible process under the conditions of the reaction.[9b] This makes formation of **3** a 'trap' for the singlet spin state of 1,4-didehydrobenzene, **2**. The alternative pathway to products, the 1,5-hydrogen atom migration, may occur from either the S or T state of **2**. In the T state, **2** is unable to open to **1** or **3**, and must proceed *via* 1,5-hydrogen atom migration that leads to the ground-state products, **4** and **5**. Any change in k_{isc} between the S and T reaction manifolds of **2** would have a pronounced effect on both the rate of product formation and the distribution of products from the thermolysis of **1**. Fig. 2 shows the invariance of the ratio of products **3**, **4** and **5** *vs.* magnetic field.

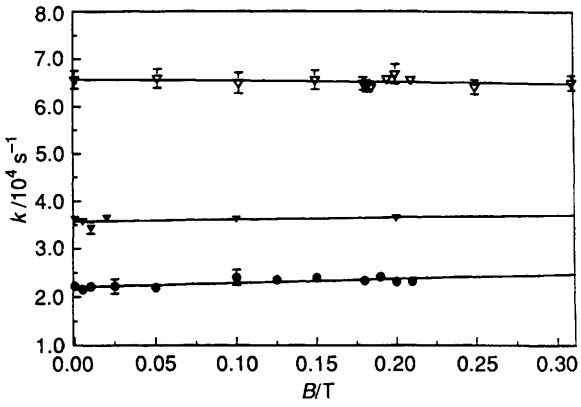


Fig. 1 First-order rate constant for the disappearance of **1** (▽), **6** (▼) and **8** (●) as a function of applied magnetic field flux. Reaction conditions follow. Compound **1**: 0.010 mol dm^{-3} in benzene, 0.010 mol dm^{-3} naphthalene (internal standard), 156 ± 0.1 °C; compound **6**: 0.010 mol dm^{-3} in benzene, 0.010 mol dm^{-3} toluene (internal standard), 0.2 mol dm^{-3} cyclohexa-1,4-diene, 196 ± 0.1 °C; compound **8**: 0.010 mol dm^{-3} in chlorobenzene, 0.010 mol dm^{-3} naphthalene (internal standard); 0.2 mol dm^{-3} cyclohexa-1,4-diene, 200 ± 0.1 °C. Standard error bars are shown unless the standard error was less than the size of the plotted symbol.

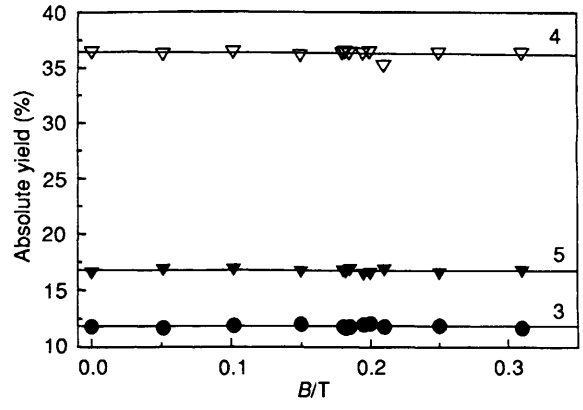
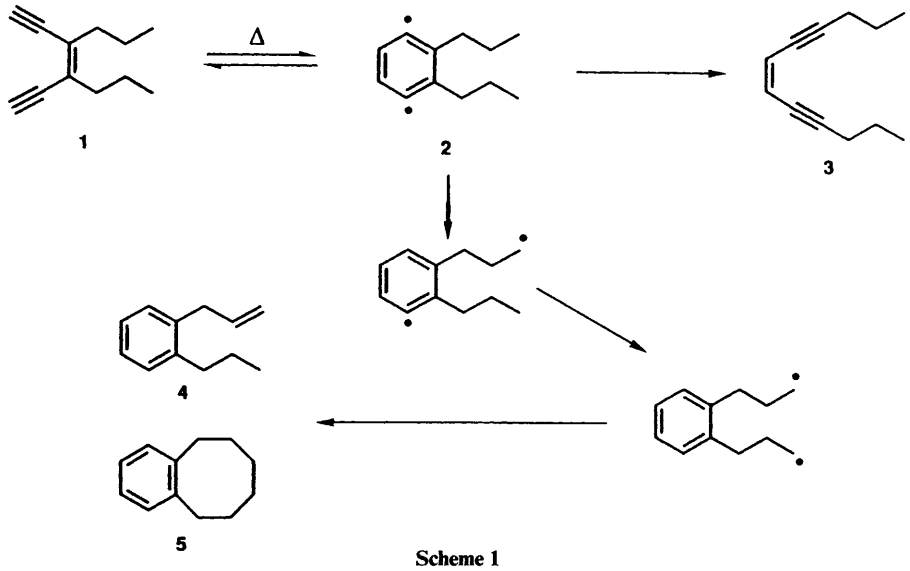


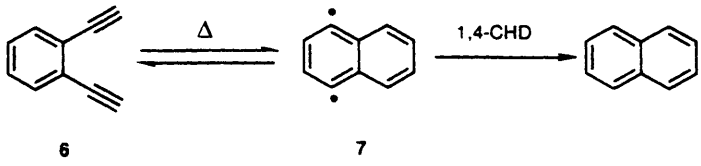
Fig. 2 Percentage of compounds **3** (●), **4** (▽) and **5** (▼) shown as a function of magnetic field flux. Reaction conditions for **1** are as described in Fig. 1.

As a probe of spin correlation in 1,4-didehydronaphthalene **7**, compound **6** was thermolysed in benzene, toluene, chlorobenzene and iodobenzene to probe for an external heavy-atom effect (Scheme 2). No significant difference in the first-order rate of disappearance of **6** was observed (data not shown). This is in agreement with the previous observation that the C : E ratio from thermolysis of the related diyl, **2**, is unchanged upon going from toluene to bromobenzene.[9b] Similarly, the rate of disappearance of **6** did not vary with applied magnetic flux density (data are similar in appearance to those presented in Fig. 1).

To allow for an ISC mechanism other than $S–T_{-1}$ level crossing, the kinetics of asymmetric enediyne **8** (Scheme 3) were determined as a function of magnetic field flux. Because Δg for organic biradicals is small, the product of $\Delta g\beta B$ is small and becomes significant only at high magnetic fields. Even at 6.6 T (corresponding to the field of a 300 MHz NMR spectrometer), no change in the kinetic rate constant for disappearance of **8** was observed.



Scheme 1



Scheme 2

Discussion

Kinetically significant intersystem crossing between the S and T surfaces has three distinct requirements: (1) the singlet **2** must be relatively long lived (lifetime > 10^{-10} s) to allow time for ISC to occur; (2) the singlet–triplet energy gap, ΔE_{S-T}, must be small to allow for transition between the reaction surfaces and (3) a physical mechanism must exist whereby ISC can occur. For a hypothetical diradical that is formed exclusively in the singlet state, but can only form product from the triplet state, a maximum threefold change in the rate of product formation might be expected.

Calculation and experiment indicate a singlet ground state for 1,4-didehydrobenzene with ΔE_{ST} of 0.5–2 kcal mol^{-1}.[12a–e] The prediction of a small ΔE_{ST} indicates the radical centres do not interact strongly. An early hypothesis was that 1,4-didehydrobenzene is a ground-state singlet because of a partial bonding interaction between the two radical centres.[12f] This suggestion has not been validated by more recent calculations that place the C1–C4 distance at 2.7 Å[12e] and constrain all C1–C4 interactions to through-bond interactions.[16]

Product analysis of the thermolysis of **1** at 200 °C suggests a lifetime of singlet **2** of only 10^{-9} s,[9a,b] although the lifetime at 156 °C is expected to be slightly longer. Even if ΔE_{ST} is small and the lifetime of 1,4-didehydrobenzene is at least 10^{-9} s, ISC can only occur if a mechanism is available that efficiently mixes the S and T surfaces. The lack of a magnetically active nucleus at the radical centre eliminates HFC from mixing the spin states. Additionally, since the radical centres in **2** and **7** are related by symmetry, they have identical Lande *g*-values. Hence, their difference Δg, is zero and they will precess about the external field at the same rate and k_{isc} induced by the Δg mechanism will be zero at all values of $\boldsymbol{B}$.

This leaves the level-crossing mechanism for magnetic field induced ISC. This mechanism has been observed mainly in biradical systems where the centres of unpaired electron density are held at a fixed distance. Of all the possible physical mechanisms for magnetic field induced ISC, degeneracy of the S_0 and T_{-1} surfaces might reasonably be expected to operate in 1,4-didehydrobenzene to mix the S and T reaction manifolds.

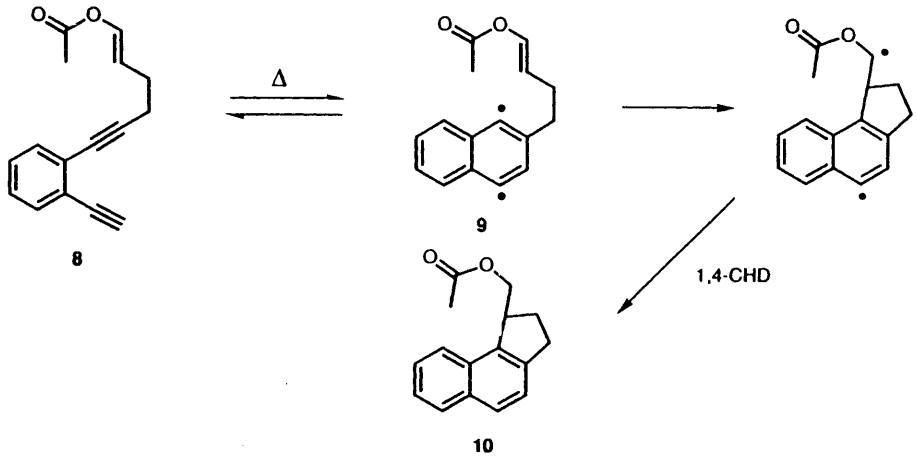
Even if the level-crossing mechanism provides a plausible pathway for ISC, a magnetic field effect may not be observed if an intramolecular pathway exists that rapidly drains away the 1,4-didehydrobenzene intermediate as it is formed. This pathway exists for intermediates **2** and **9**.

The thermolysis of **6** provides an example of the Bergman cycloaromatization reaction without an intramolecular trap for the singlet 1,4-didehydronaphthalene intermediate. 1,4-CHD was present in 20-fold excess to provide an intermolecular hydrogen atom source to ensure that naphthalene would be the only product. The singlet 1,4-didehydronaphthalene biradical intermediate, **7**, can partition between an intramolecular ring-opening pathway to regenerate **6**, and an intermolecular pathway involving H• abstraction to produce naphthalene. Only the intramolecular pathway (reversion to **6**) requires the S spin state. Intersystem crossing to triplet **7** would extend the lifetime of the 1,4-didehydrobenzene intermediate and favour the intermolecular reaction pathway and lead to an increased overall rate of naphthalene production.

Ab initio (CASSCF) calculation of geometries along the reaction coordinate to the formation of 1,4-didehydrobenzene from hex-3-ene-1,5-diyne suggest that diyl formation may not be concerted and may not be triggered merely by bringing the incipient diyl centres to a bond-forming distance.[17] An alternative model would require abstraction of the first hydrogen atom to be synchronous with cycloaromatization. In this scenario, a discrete diyl does not exist. This proposal is consistent with an observed absence of inducible ISC (this report) and the lack of observable CIDNP arising directly from the 1,4-diyl.[9a]

Conclusions

When we initiated this study, our goal was not only to probe the spin state of 1,4-didehydrobenzene, but also to investigate the possibility of providing a method for rate control and product selectivity. Such features would be beneficial in many



Scheme 3

aspects of enediyne cycloaromatizations as they are currently being exploited. The results reported herein are significant in that regard, since they eliminate the possibility of using laboratory magnetic fields to manipulate the activity of enediynes in synthetic and pharmaceutical pursuits.

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References

1 Calicheamicin: (*a*) M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3464; (*b*) M. D. Lee, T. S. Dunne, G. A. Ellestad, M. M. Siegel, C. C. Chang, G. O. Morton, W. J. McGahren and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3466; (*c*) M. D. Lee, G. A. Ellestad and D. B. Borders, *Acc. Chem. Res.*, 1992, **24**, 235.

2 Esperamicin: (*a*) M. Konishi, H. Ohkuma, K. Saitoh, H. Kaweguchi, J. Golik, G. Dubay, G. Groenewold, B. Krishnan and T. W. Doyle, *J. Antibiot.*, 1985, **38**, 1605; (*b*) J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3461.

3 Dynemicin: (*a*) M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Mamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. Van Duyne and J. Clardy, *J. Antibiot.*, 1989, **42**, 1449; (*b*) M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, T. Oki, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3715.

4 Neocarzinostatin: (*a*) A. G. Myers, *Tetrahedron Lett.*, 1987, **28**, 4493; (*b*) A. G. Myers, P. J. Proteau and T. M. Handel, *J. Am. Chem. Soc.*, 1988, **110**, 7212; (*c*) A. G. Myers, P. S. Dragovich and E. Y. Kuo *J. Am. Chem. Soc.*, 1992, **114**, 9369; (*d*) I. H. Goldberg, *Acc. Chem. Res.*, 1991, **24**, 191; (*e*) I. H. Goldberg and M. Rabinowitz, *Science*, 1962, **136**, 315.

5 Kedarcidin: J. E. Leet, D. R. Schroeder, S. L. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohy, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc.*, 1992, **114**, 7946.

6 For examples of synthetic DNA cleaving agents based upon the reactive 1,4-didehydrobenzene intermediate, see: (*a*) K. C. Nicolaou, W.-M. Dai, S.-C. Tsay, V. A. Estevez and W. Wrasidlo, *Science*, 1992, **256**, 1172; (*b*) K. C. Nicolaou, P. Maligres, T. Suzuki, S. V. Wendeborn, W.-M. Dai and R. K. Chadha, *J. Am. Chem. Soc.*, 1992, **114**, 8890; (*c*) K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1387; (*d*) K. C. Nicolaou and W.-M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 8908; (*e*) K. C. Nicolaou and A. L. Smith, *Acc. Chem. Res.*, 1992, **25**, 497; (*f*) K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez and W.-M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 7360.

7 (*a*) J. W. Grissom and T. L. Calkins, *Tetrahedron Lett.*, 1992, **33**, 2315; (*b*) J. W. Grissom and T. L. Calkins, *J. Org. Chem.*, 1993, **58**, 5422; (*c*) J. W. Grissom, T. L. Calkins and M. Egan, *J. Am. Chem. Soc.*, 1993, **115**, 11744; (*d*) J. W. Grissom, T. L. Calkins and H. A. McMillen, *J. Org. Chem.*, 1993, **58**, 6556; (*e*) J. W. Grissom and D. Klingberg, *J. Org. Chem.*, 1993, **58**, 6559.

8 R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.*, 1973, **94**, 660.

9 (*a*) T. P. Lockhart, P. B. Comita and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4082; (*b*) T. P. Lockhart and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4091; (*c*) T. P. Lockhart, C. B. Mallon and R. G. Bergman, *J. Am. Chem. Soc.*, 1980, **102**, 5976; (*d*) R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25.

10 Intermolecular and intramolecular heavy-atom effects in spin-correlated radical pair and biradical reactions occur because of an increase in ISC induced by the large spin orbit coupling (SOC) of atoms such as Br and I. For a discussion of the heavy-atom induced ISC, see: (*a*) I. V. Khudyakov, Y. A. Serebrennikov and N. J. Turro, *Chem. Rev.*, 1993, **93**, 537; (*b*) N. J. Turro, *Modern Molecular Photochemistry*, Univ. Science Books, Mill Valley, CA, 1991, p. 192.

11 O. L. Chapman, C. C. Chang and J. Kolc, *J. Am. Chem. Soc.*, 1976, **98**, 5703.

12 (*a*) A. Nicolaides and W. T. Borden, *J. Am. Chem. Soc.*, 1993, **115**, 11951; (*b*) S. G. Wierschke, J. J. Nash and R. R. Squires, *J. Am. Chem. Soc.*, 1993, **115**, 11958; (*c*) P. G. Wenthold, J. A. Paulino and R. R. Squires, *J. Am. Chem. Soc.*, 1991, **113**, 7414; (*d*) M. J. S. Dewar, G. P. Ford and C. H. Reynolds, *J. Am. Chem. Soc.*, 1983, **105**, 3162; (*e*) J. D. Noell and M. D. Newton, *J. Am. Chem. Soc.*, 1979, **101**, 51; (*f*) M. J. S. Dewar and W.-K. Li, *J. Am. Chem. Soc.*, 1974, **96**, 5569.

13 For reviews on magnetic field effects see: (*a*) H. Hayashi, in *Photochemistry and Photophysics*, ed. J. F. Rabek, CRC Press, Boca Raton, Florida, 1990, vol. 1, ch. 2; (*b*) U. E. Steiner and H.-J. Wolff, in *Photochemistry and Photophysics*, ed. J. F. Rabek, CRC Press, Boca Raton, Florida, 1990, vol. 4, ch. 1; (*c*) U. E. Steiner and T. Ulrich, *Chem. Rev.*, 1989, **89**, 51; (*d*) K. M. Salikhov, Y. M. Molin, R. Z. Sagdeev and A. L. Buchachenko, 'Spin Polarization and Magnetic Effects' in *Radical Reactions*, Elsevier, Amsterdam, 1984; (*e*) N. J. Turro, *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 609; (*f*) C. Doubleday Jr., N. J. Turro and J.-F. Wang, *Acc. Chem. Res.*, 1989, **22**, 199.

14 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon, New York, 1980.

15 M. F. Semmelhack, T. Neu and F. Foubelo, *Tetrahedron Lett.*, 1992, **33**, 3277.

16 Through-space orbital interactions are limited to 2.5 Å or less: (*a*) R. Hoffmann, *Acc. Chem. Res.*, 1971, **4**, 1; R. Hoffmann, A. Imamura and W. J. Hehre, *J. Am. Chem. Soc.*, 1968, **90**, 1499.

17 R. Lindh and J. J. Persson, *J. Am. Chem. Soc.*, 1994, **116**, 4963.

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